Remarks

Claims 1-7, 12-14, 16, 17, 19, 21, 24, 25, 28, 30, 32, 35, 38, 39, 49, 51, 59 and 75 were pending in the subject application. By this amendment, applicants have canceled all the claims and added new claims 76-133. New claims 76-82 correspond to canceled claims 1-7; new claims 87-89 correspond to canceled claims 12-14; new claims 91, 92, 94, 96, 99 and 100 correspond to canceled claims 16, 17, 19, 21, 38 and 39, respectively; new claim 110 corresponds to canceled claim 49; new claim 111 corresponds to canceled claim 51; new claim 116 corresponds to canceled claim 59; and new claim 133 corresponds to canceled claim 75. Accordingly, claims 76-133 are currently pending.

The R groups in the structures and definitions appearing on pages 10-11, 55-63, 67, 69 and 80 have been amended in order to make the numbering scheme consistent throughout the specification. The elected claims have been rewritten for the same reason. Support for the changes can be found inter alia in the specification, as originally filed, on pages 16, 20 and 93 where the structures appear with the correct numbering of the R groups. Other than the renumbering, no changes have been made to the definitions of the R groups. Hence, no new matter is being introduced.

Page 15 of the specification has been amended to correct the misspelling of glaucoma. Page 15 has also been amended to replace the phrase "comprising the compound of claims 1, 6, or 18" with the phrase "comprising a compound of structure IV, V or VI." Support for the changes can be found in claims 1, 6 and 18 as originally filed and inter alia on pages 60, 62 and 67 of the specification.

The paragraphs added to the subject specification on page 43 are taken from pages 355-358 of R.B. Silverman, 1992, "The Organic

Chemistry of Drug Design and Drug Action," Academic Press, Chapter 8, which is incorporated by reference on page 43, line 9 of the specification. A copy of the aforementioned pages is attached hereto as **Exhibit B**. No new matter is introduced.

Support for new claim 76 may be found inter alia in the specification, on page 69, lines 1-24.

Support for new claim 77 may be found inter alia in the specification, on page 69, lines 26-35.

Support for new claim 78 may be found inter alia in the specification, as originally filed, on page 70, lines 1-15.

Support for new claim 79 may be found inter alia in the specification, as originally filed, on page 70, lines 19-35.

Support for new claim 80 may be found inter alia in the specification, as originally filed, on page 71, lines 1-15.

Support for new claim 81 may be found inter alia in the specification, as originally filed, on page 72, lines 1-15.

Support for new claim 82 may be found inter alia in the specification, as originally filed, on page 72, lines 22-35.

Support for new claim 83 may be found inter alia in the specification, as originally filed, on page 73, lines 1-10.

Support for new claim 84 may be found inter alia in the specification, as originally filed, on page 73, lines 12-23.

Support for new claim 85 may be found inter alia in the

specification, as originally filed, on page 73, lines 25-37.

Support for new claim 86 may be found inter alia in the specification, as originally filed, on page 74, lines 1-15.

Support for new claim 87 may be found inter alia in the specification, as originally filed, on page 74, lines 15-32.

Support for new claim 88 may be found inter alia in the specification, as originally filed, on page 75, lines 1-15.

Support for new claim 89 may be found inter alia in the specification, as originally filed, on page 75, lines 19-32.

Support for new claim 90 may be found inter alia in the specification, as originally filed, on page 76, lines 1-13.

Support for new claim 91 may be found inter alia in the specification, as originally filed, on page 76, lines 19-32.

Support for new claim 92 may be found inter alia in the specification, as originally filed, on page 77, lines 1-15.

Support for new claim 93 may be found inter alia in the specification, as originally filed, on page 77, lines 20-33.

Support for new claim 94 may be found inter alia in the specification, as originally filed, on page 78, lines 1-15.

Support for new claim 95 may be found inter alia in the specification, as originally filed, on page 78, lines 18-30.

Support for new claim 96 may be found inter alia in the specification, as originally filed, on page 79, lines 1-12.

Support for new claim 97 may be found inter alia in the specification, as originally filed, on page 79, lines 15-25.

Support for new claim 98 may be found inter alia in the specification, as originally filed, on page 79, lines 27-38.

Support for new claim 99 may be found inter alia in the specification, as originally filed, on page 61, lines 26-35.

Support for new claim 100 may be found inter alia in the specification, as originally filed, on page 87, lines 18-21, and page 88, lines 2-5.

Support for new claim 101 may be found inter alia in the specification, as originally filed, on page 87, line 23.

Support for new claim 102 may be found inter alia in the specification, as originally filed, on page 87, line 25.

Support for new claim 103 may be found inter alia in the specification on page 43, lines 7-30 and in the inserted paragraphs from R.B. Silverman.

Support for new claim 104 may be found inter alia in the specification, as originally filed, on page 88, lines 21-24.

Support for new claim 105 may be found inter alia in the specification, as originally filed, on page 88, lines 26-27.

Support for new claim 106 may be found inter alia in the specification, as originally filed, on page 88, lines 29-31.

Support for new claim 107 may be found inter alia in the specification, as originally filed, on page 89, lines 4-5.

Support for new claim 108 may be found inter alia in the specification, as originally filed, on page 89, lines 7-9.

Support for new claim 109 may be found inter alia in the specification, as originally filed, on page 89, lines 11-12.

Support for new claim 110 may be found inter alia in the specification, as originally filed, on page 88, lines 33-36 and on page 18, line 32 to page 19, line 36.

Support for new claim 111 may be found inter alia in the specification, as originally filed, on page 89, lines 14-17, page 87, lines 27-28, and page 88, lines 11-12.

Support for new claim 112 may be found inter alia in the specification, as originally filed, on page 89, line 19.

Support for new claim 113 may be found inter alia in the specification, as originally filed, on page 89, line 21.

Support for new claim 114 may be found inter alia in the specification, as originally filed, on page 89, lines 26-29 and on page 39, lines 27-29.

Support for new claim 115 may be found inter alia in the specification, as originally filed, on page 89, line 35.

Support for new claim 116 may be found inter alia in the specification, as originally filed, on page 50, lines 6-23, on page 12, line 27, on page 14, lines 24-27, and on page 90, lines 3-6.

Support for new claim 117 may be found inter alia in the specification, as originally filed, on page 87, lines 18-21, and

line 27 to page 88, line 13.

Support for new claim 118 may be found inter alia in the specification, as originally filed, on page 90, line 17.

Support for new claim 119 may be found inter alia in the specification, as originally filed, on page 87, lines 18-21, 29 and on page 50, lines 9-16.

Support for new claim 120 may be found inter alia in the specification, as originally filed, on page 90, line 17.

Support for new claim 121 may be found inter alia in the specification, as originally filed, on page 89, line 31.

Support for new claim 122 may be found inter alia in the specification, as originally filed, on page 50, line 11.

Support for new claim 123 may be found inter alia in the specification, as originally filed, on page 15, lines 26-29.

Support for new claim 124 may be found inter alia in the specification, as originally filed, on page 90, lines 22-25.

Support for new claim 125 may be found inter alia in the specification, as originally filed, on page 90, lines 26-29.

Support for new claim 126 may be found inter alia in the specification, as originally filed, on page 90, lines 31-32.

Support for new claim 127 may be found inter alia in the specification, as originally filed, on page 90, lines 34-36.

Support for new claim 128 may be found inter alia in the

specification, as originally filed, on page 90, line 38 to page 91, line 1.

Support for new claim 129 may be found inter alia in the specification, as originally filed, on page 91, lines 3-5.

Support for new claim 130 may be found inter alia in the specification, as originally filed, on page 91, lines 7-8.

Support for new claim 131 may be found inter alia in the specification, as originally filed, on page 91, lines 10-12.

Support for new claim 132 may be found inter alia in the specification, as originally filed, on page 91, lines 14-19.

Support for new claim 133 may be found inter alia in claim 75 as originally filed.

Restriction Requirement

In the Restriction Requirement issued on September 27, 2002, the Examiner required restriction to one of the following allegedly distinct inventions as follows:

I. Claims 1-7, 12-14, 16-17, 19, 21, 38 and 75, drawn to 7-deaza-2-benzyl substituted purine compounds and method for making the same;

II. Claims 24, 25, 28, 30, 32 and 35, drawn to 7-deaza-2-benzyl-6-heterocyclic substituted purine compounds;

III. Claims 39 and 49 drawn to a method for treating a disease associated with an A3 adenosine receptor in a subject (patient or cell);

IV. Claim 51 drawn to a method for treating gastrointestinal disorder by administering a compound of Invention I or II;

V. Claim 59, drawn to a method for treating eye damage by administering a compound of Invention I or II.

The Examiner alleged that inventions I and II are unrelated as they identify two distinct compositions of matter as Invention II contains an additional heterogroup. The Examiner also alleged that the process in Invention I will not produce the compounds of Invention II. The Examiner further alleged that Inventions I and III, IV and V, and Inventions II and III, IV and V are related as product and process of use. The Examiner alleged that the Inventions are distinct because the products of Inventions I and II may be used in materially different methods than those of inventions III, IV and V. The Examiner further alleged that Inventions III, IV and V are unrelated because they possess different functions. The Examiner alleged that while the function of Invention of Invention III is to treat diseases associated with A3 adenosine receptor cells, the functions of Inventions IV and V, as claimed, are not limited to treatment of diseases associated with A3 adenosine receptor cells. Specifically, the Examiner alleged that the functions of Inventions IV and V are treating of gastrointestinal disorder and damage to the eye, respectively, neither of which need be A3 adenosine receptor related. In addition, the Examiner alleged that the Inventions produce different effects. The Examiner stated that Applicant is entitled to one composition of matter and one method for using the same. The Examiner stated that a method will be examined insofar as it relates to the elected composition of matter.

In response, applicants hereby elect, with traverse, Invention I, new claims 76-99 and 133, for the purpose of preliminary examination.

Applicants, however, respectfully request that the Examiner reconsider and withdraw the restriction requirement with respect

to Inventions I, III, IV and V.

With regard to the relation between Invention I and Inventions III, IV and V, applicants draw the Examiner's attention to M.P.E.P. Section 806.05(h) which states, in part,

> A product and a process of using the product can be shown to be distinct inventions if either or both of the following can be shown: (A) the process of using as claimed can be practiced with another materially different product; or (B) the product as claimed can be used in a materially different process.
>
> The burden is on the examiner to provide an example, but the example need not be documented. (Emphasis added)

The Examiner alleged that the products of Inventions I and II may be used in materially different methods than those of Inventions III, IV and V. However, the Examiner failed to provide an example of any such use. The mere statement by the Examiner that the compounds may be used in materially different methods is insufficient basis on which to ground a restriction. Thus, applicants contend that the restriction between Inventions I and II and Inventions III, IV and V is improper.

Furthermore, applicants note that M.P.E.P. §806.05(h) does not address how to treat such claims once the product claim is allowed. M.P.E.P. § 806.05(i) addresses how to treat such claims once the product claim is allowed:

> Where the product claims are allowable (i.e., novel and nonobvious), restriction may be required only where the process of making and the product made are distinct (MPEP § 806.05(f)); otherwise, *the process of using must be joined with the process of making and product made, even if a showing of distinctness can be*

made between the product and process of using (MPEP § 806.05(h)). (Emphasis added)

Indeed, such treatment of the claims is rational in view of the minimal burden on the Examiner to examine process of use claims which incorporate all of the limitations of an allowed product claim. Consequently, applicants maintain that even if the restriction of Invention I from Inventions III, IV and V is maintained for the purpose of preliminary examination, Inventions III, IV and V should be rejoined and examined once the product claims are found allowable.

Furthermore, claim 76 is a linking claim that links the inventions of Groups I, III, IV and V according to M.P.E.P. § 809.03. Pursuant to M.P.E.P. § 809.04 "*[I]f a linking claim is allowed, the examiner must thereafter examine* species if the linking claim is generic thereto, or he or she must examine *the claims to the nonelected inventions that are linked* to the elected invention by such allowed linking claim." (Emphasis added). Therefore, applicants hereby respectfully request that the Examiner examine nonelected Inventions III, IV and V once the linking claim of Invention I is found allowable.

With regard to Inventions III, IV and V, applicants have rewritten claims 51 and 59 as new claims 111 and 116, respectively. The new claims recite the limitation "...disorder associated with an A3 adenosine receptor..." Consequently, the claims of Inventions III, IV and V now all serve the same function, namely, the treatment of diseases associated with the A3 adenosine receptor. Furthermore, applicants contend the mode of operation of the compounds in the claimed uses is the same. The compounds all bind to the A3 adenosine receptor. This binding subsequently leads to numerous secondary effects. However,

applicants contend that they are only claiming one utility, the inhibition of the A3 adenosine receptor.

In addition, applicants draw the Examiner's attention to M.P.E.P. Section 803, which states in part,

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. (Emphasis added)

Applicants contend that there is no serious burden on the Examiner to examine the claims of Invention I along with the claims of Inventions III-V because a search for the claimed compounds would necessarily find uses of any such compounds.

In view of the preceding discussion, applicants respectfully request that the Examiner reconsider and withdraw the restriction requirement in its entirety.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Response to Notice of Non-Compliant Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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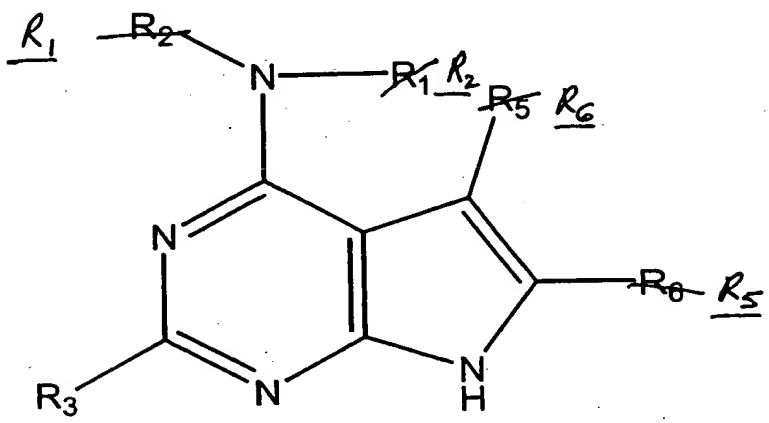
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents
Washington, DC 20231

Gary J. Gershik 12/11/02

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

antagonist of A_{2b}). Preferably, the animal is a human.

This invention also features a compound having the structure:



wherein R_1 is H and R_2 is cyclopropyl methylamino carbonylethyl, *cis*-3-hydroxy cyclopentyl, acetamido butyl, methylamino carbonylamino butyl, ethylamino carbonylamino propyl, methylamino carbonylamino propyl, 2-acetyl amino-3-methyl butyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, N-methylaminocarbonyl pyridyl-2- methyl, or R_1, R_2 and the nitrogen together are 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino.

wherein R_3 is a substituted or unsubstituted four to six menbered ring, pyrrole, thiophene, furan, thiazole, imidazole, pyrazole, 1,2,4-triazole, pyridine, 2(1H)-pyridone, 4(1H)-pyridone, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, tetrazole,

naphthalene, tetralin, naphthyridine, benzofuran, benzothiophene, indole, 2,3-dihydroindole, 1H-indole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole, purine, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyrazine, pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, purido[3,4-b]-pyridine, 1H-pyrazole[3,4-d]pyrimidine, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 1,4-benzisoxazine, benzothiazole, quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzoxazine, phthalazine, or cinnoline.

wherein ~~R_5~~ R_6 is H, alkyl, substituted alkyl, or cycloalkyl; and

wherein ~~R_6~~ R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl; and

This invention also features a method for inhibiting the activity of an A_3 adenosine receptor in a cell, which comprises contacting said cell with the above-mentioned compounds.

Other therapeutic applications of the compounds of the invention include treatment of obesity (lipolytic properties), hypertension, treatment of depression, sedative, anxiolytic, as antileptics and as laxatives, e.g., effecting motility without causing diarrhea.

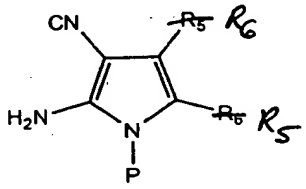
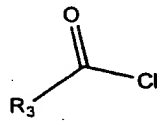
The term "disease state" is intended to include those conditions caused by or associated with unwanted levels of adenosine, adenylyl cyclase activity, increased physiological activity associated with aberrant stimulation of adenosine receptors and/or an increase in cAMP. In one embodiment, the disease state is, for example, asthma, chronic obstructive pulmonary disease, allergic rhinitis, bronchitis, renal disorders, gastrointestinal disorders, or eye disorders. Additional examples include chronic bronchitis and cystic fibrosis. Suitable examples of inflammatory diseases include non-lymphocytic leukemia, myocardial ischaemia, angina, infarction, cerebrovascular ischaemia, intermittent claudication, critical limb ischemia, venous hypertension, varicose veins, venous ulceration and arteriosclerosis. Impaired reperfusion states include, for example, any post-surgical trauma, such as reconstructive surgery, thrombolysis or angioplasty.

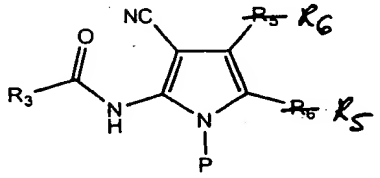
This invention also provides a combination therapy for ~~glycoma~~ glaucoma, comprising ~~the~~ a compound of ~~claims 1, 6, or 10,~~ structure III, II or VII, and a prostagladin agonist, β2-2 agonist, or a muniscrinic antagonist.

The language "treatment of a N-6 substituted 7-deazapurine responsive state" or "treating a N-6 substituted 7-deazapurine responsive state" is intended to include changes in a disease state or condition, as described above, such that physiological symptoms in a mammal can be significantly diminished or minimized. The language also includes control, prevention or inhibition of physiological symptoms or effects

typical practice and is known to those skilled in the art. Typical synthetic schemes for the preparation of deazapurine intermediates of the invention are outlined below in Scheme I.

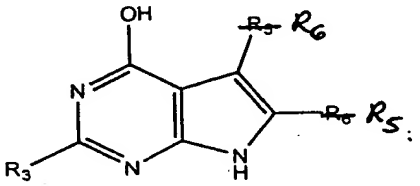
This invention also provides a method of preparing compound IV, comprising the steps of

a) reacting  and 

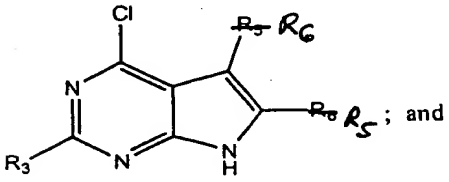
to provide 

wherein P is a removable protecting group;

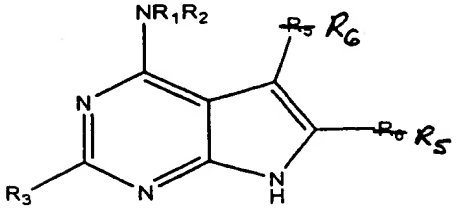
b) treating the product of step a) under cyclization conditions to provide



c) treating the product of step b) under suitable conditions to provide

 ; and

d) treating the chlorinated product of step c) with NHR_1R_2 to provide



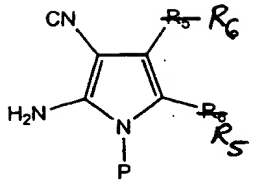
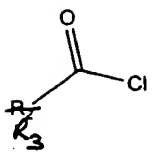
wherein R_1 is H and R_2 is cyclopropyl methylamino carbonylethyl, *cis*-3-hydroxy cyclopentyl, acetamido butyl, methylamino carbonylamino butyl, ethylamino carbonylamino propyl, methylamino carbonylamino propyl, 2-acetyl amino-3-methyl butyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, N-methylaminocarbonyl pyridyl-2- methyl, or R_1, R_2 and the nitrogen together are 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino.

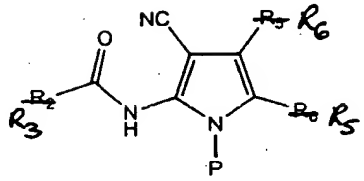
wherein R_3 is a substituted or unsubstituted four to six membered ring;

wherein ~~R_5~~ R_6 is H, alkyl, substituted alkyl, or cycloalkyl; and

wherein ~~R_6~~ R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl; and

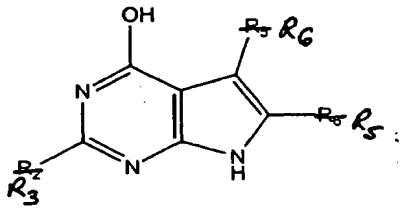
This invention also provides a method of preparing compound of V, comprising the steps of

a) reacting  and 

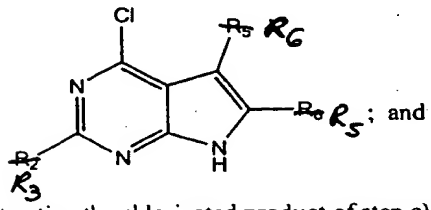
to provide 

wherein P is a removable protecting group;

b) treating the product of step a) under cyclization conditions to provide

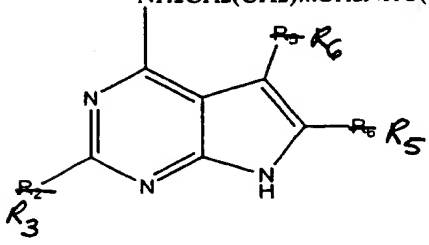


c) treating the product of step b) under suitable conditions to provide

 ; and

d) treating the chlorinated product of step c) with $NH_2CH_2(CH_2)_mCH_2NHC(=O)R_1$ to provide

$NH_2CH_2(CH_2)_mCH_2NHC(=O)R_1$



wherein m is 0, 1, or 2;

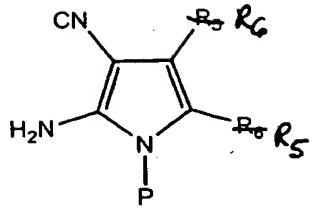
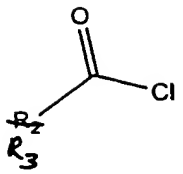
wherein R_1 is cyclopropyl methyl, methyl, methylamino, or aminomethyl;

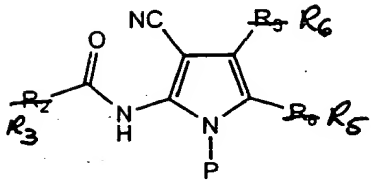
wherein ~~R_2~~ R_3 is aryl, substituted aryl, heteroaryl;

wherein ~~R_5~~ R_6 is H, alkyl, substituted alkyl, or cycloalkyl;

wherein ~~R_6~~ R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and the nitrogen together form a ring system of between 4 and 7 members; and

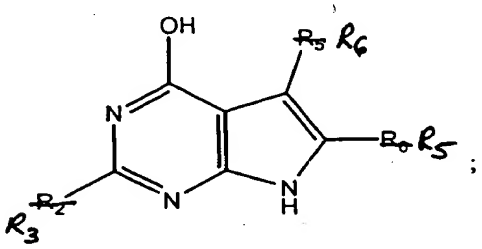
This invention further provided a method of preparing compound VI, comprising

a) reacting  and 

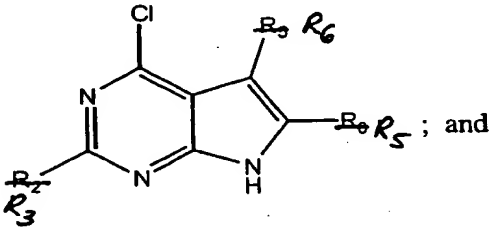
to provide 

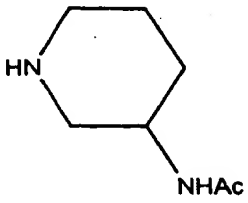
wherein P is a removable protecting group;

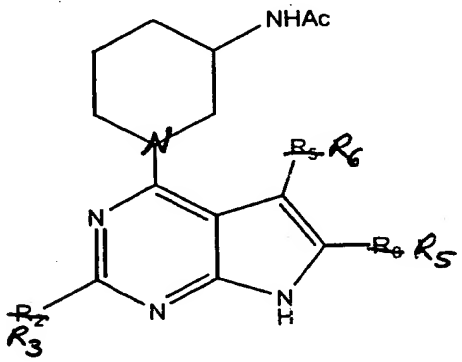
b) treating the product of step a) under cyclization conditions to provide

 ;

c) treating the product of step b) under suitable conditions to provide

 ; and

d) treating the chlorinated product of step c) with 

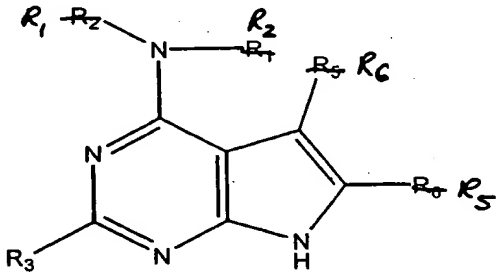
to provide 

wherein ~~R_2~~ R_3 is unsubstituted aryl.

wherein ~~R_5~~ R_6 is H, alkyl, substituted alkyl, or cycloalkyl;

wherein ~~R_6~~ R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and the nitrogen together form a ring system of between 4 and 7 members; and

This invention also provides a compound having the structure:



IV

wherein R_1 is H and R_2 is cyclopropyl methylamino carbonylethyl, *cis*-3-hydroxy cyclopentyl, acetamido butyl, methylamino carbonylamino butyl, ethylamino carbonylamino propyl, methylamino carbonylamino propyl, 2-acetyl amino-3-methyl butyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, N-methylaminocarbonyl pyridyl-2- methyl, or R_1, R_2 and the nitrogen together are 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl

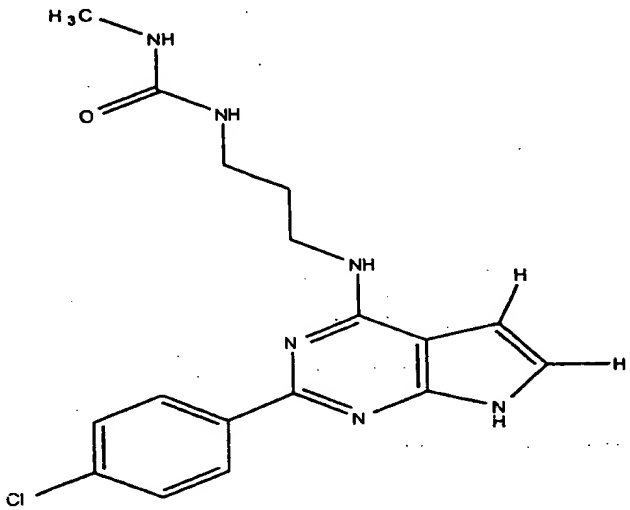
piperadino; and

wherein R_3 is a substituted or unsubstituted benzene, pyrrole, thiophene, furan, thiazole, imidazole, pyrazole, 1,2,4-triazole, pyridine, 2(1H)-pyridone, 4(1H)-pyridone, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, tetrazole, naphthalene, tetralin, naphthyridine, benzofuran, benzothiophene, indole, 2,3-dihydroindole, 1H-indole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole, purine, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyrazine, pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, purido[3,4-b]-pyridine, 1H-pyrazole[3,4-d]pyrimidine, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 1,4-benzisoxazine, benzothiazole, quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzoxazine, phthalazine, or cinnoline.

wherein ~~R_6~~ R_6 is H, alkyl, substituted alkyl, or cycloalkyl;

wherein ~~R_6~~ R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl; and

In one embodiment of the compound, the compound has the structure:

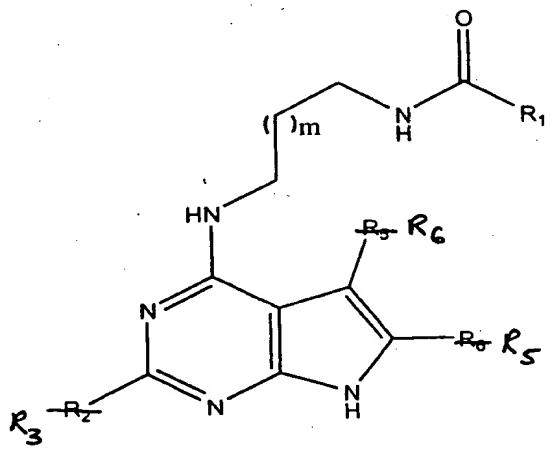


In another embodiment of the compound, R_3 is phenyl.

In another embodiment of the compound, ~~R_5~~ R_6 is hydrogen or methyl.

In another embodiment of the compound, ~~R_6~~ R_5 is hydrogen, methyl, phenyl, 3-chlorophenyloxy methyl, or *trans*-2- phenylamino methyl pyrrolidino methyl.

This invention further provides a compound having the structure:



V

wherein m is 0, 1, or 2;

wherein R_1 is cyclopropyl methyl, methyl, methylamino, or aminomethyl;

wherein ~~R_2~~ R_3 is aryl, substituted aryl, or heteroaryl;

wherein ~~R_5~~ R_6 is H, alkyl, substituted alkyl, or cycloalkyl;

wherein ~~R_6~~ R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or

cycloalkyl, or R_7, R_8 and the nitrogen together form a ring system of between 4 and 7 members; and

In one embodiment of compound V, m is 0 and R_3 is phenyl.

In another embodiment of compound V, m is 1 and R_3 is phenyl.

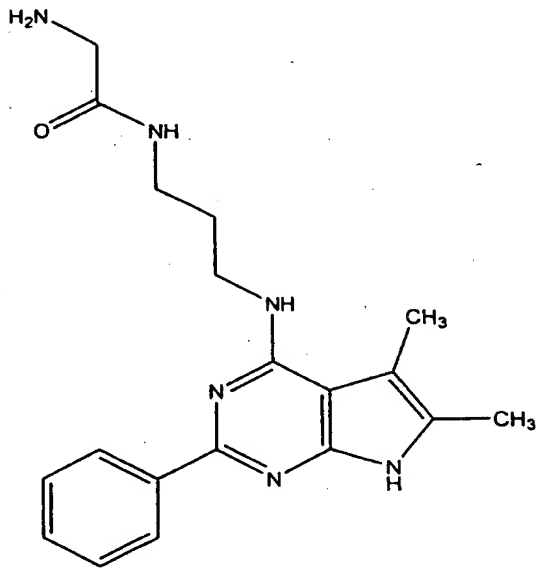
In another embodiment of compound V, m is 2 and R_3 is phenyl.

In another embodiment of compound V, R_5 and R_6 are methyl.

In another embodiment of compound V, R_5 and R_6 are methyl.

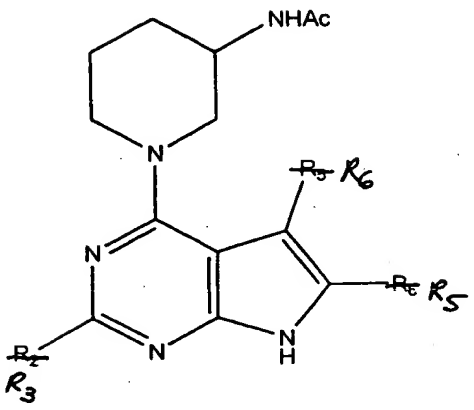
In another embodiment of compound V, R_5 and R_6 are methyl.

In another embodiment of compound V, the compound has the structure:



(Compound 1316)

This invention also provides a compound having the structure:



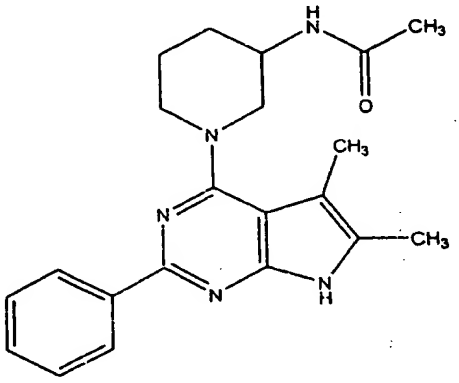
VI

wherein R3 is unsubstituted aryl.

wherein R6 is H, alkyl, substituted alkyl, or cycloalkyl;

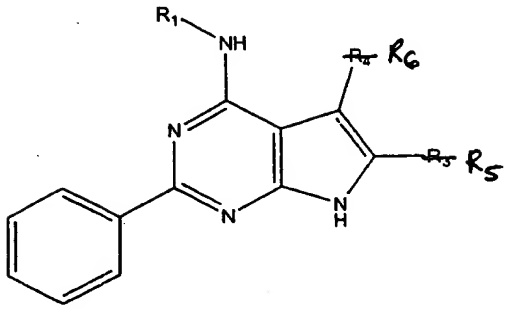
wherein R5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and the nitrogen together form a ring system of between 4 and 7 members; and

In one embodiment of compound VI, the compound has the structure:



(Compound 1309)

This invention also provides a compound having the structure:

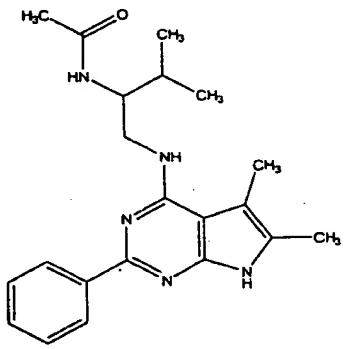


VII

wherein R_1 is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, or N-methylaminocarbonyl pyridyl-2- methyl;

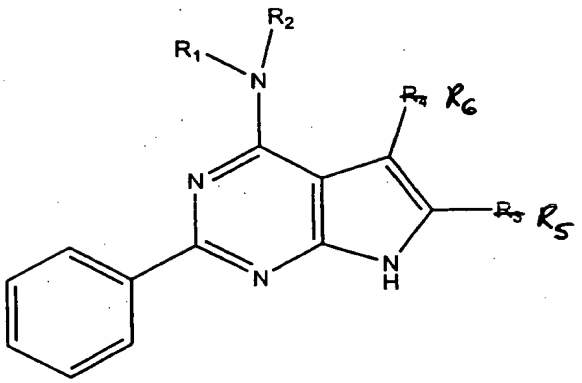
wherein ~~R_5~~ R_5 and ~~R_6~~ R_6 are independently H, substituted or unsubstituted alkyl, or aryl.

In one embodiment of the compound, the compound has the structure:



(Compound 1700)

This invention also provides a compound having the structure:

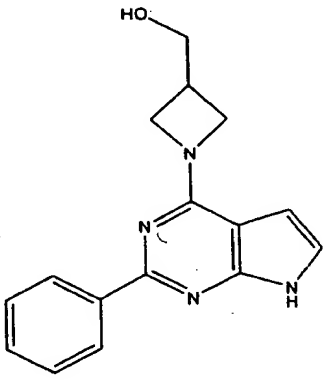


VIII

wherein R_1, R_2 and the nitrogen together are 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino;

wherein ~~R_3~~ R_5 and ~~R_4~~ R_6 are independently H, substituted or unsubstituted alkyl, or aryl.

In one embodiment of the compound, the compound has the structure:



(Compound 1711)

Compound 1707 (Table 15 below): MS(ES): 347.0 (M^++1).

Compound 1708 (Table 15 below): MS (ES) 399.0 (M^++1).

Compound 1709 (Table 15 below): MS (ES) 385.9 (M^++1).

Compound 1710 (Table 15 below): MS (ES) 434.0 (M^++1).

Compound 1711 (Table 15 below): ^{1}H-NMR (200MHz, CD_3OD) d 3.95 (d, 2H, J = 5.8Hz), 4.23 - 4.31 (m, 2H), 4.53 (t, 2H, J = 8.8Hz), 6.30 (d, 1H, J = 3.0Hz), 6.98 (d, 1H, J = 3.0Hz), 7.45 - 7.48 (m, 3H), 7.83 - 8.42 (m, 2H), 9.70 (brs, 1H). MS (ES): 281.1 (M^++1)

→Compound 1712 (Table 15 below):
~~OSIC-148313~~ ^{1}H-NMR (200MHz, CD_3OD) d 3.02 (m, 2H), 3.92 (m, 2H), 5.09 (2, 2H), 6.53 (s, 1H), 6.90-7.04 (br s, 1H), 6.92 (m, 2H), 7.02 (m, 1H), 7.21 (dd, 1H, J = 8.2Hz), 7.40 (m, 3H), 7.50-7.80 (br s, 1H), 8.33 (m, 2H). MS (ES): 445.1 (M^++1).

Compound 1713 (Table 15 below): ^{1}H-NMR (200MHz, $CDCl_3$) d 1.65-1.80(m, 7H), 1.88-2.00(m, 1H), 2.10 - 2.40 (m, 1H), 2.70-3.05 (m, 3H), 3.09-3.14 (m, 2H), 3.16-3.38 (m, 1H), 3.45 (d, 1H, J = 14Hz), 3.53-3.60 (m, 2H), 3.84-3.92 (m, 2H), 3.97 (d, 1H, J = 14Hz), 5.55 (t, 1H, J = 5.8Hz), 6.17 (s, 1H), 6.55-6.59 (m, 2H), 6.64-6.71 (m, 1H), 7.11-7.19 (m, 2H), 7.43-7.46 (m, 3H), 8.38-8.42 (m, 2H), MS (ES): 484.0 (M^++1).

Compound 1714 (Table 15 below): MS (ES): 471.0 (M^++1).

Compound 1715 (Table 15 below): MS (ES): 505.0 (M^++1).

Compound 1716 (Table 15 below): ^{1}H-NMR (200MHz, CD_3OD) d 1.65 (m, 1H), 2.18 (m, 1H), 2.49 (br d, 2H, J = 6.2Hz), 2.64 (m, 1H), 3.38 (m, 1H), 3.69 (s, 3H), 3.72 (m, 1H), 3.93 (m, 1H), 4.10 (m, 1H), 5.06 (2, 2H), 6.58 (s, 1H), 6.92 (m, 2H), 7.02 (m, 1H), 7.23 (dd, 1H, J = 8.1Hz), 7.39 (m, 3H), 8.32 (m,